Peer Review
Experimental Toxicology Division
NHEERL

MODELING

Biologically-based Modeling of Arsenic Kinetics and Dynamics

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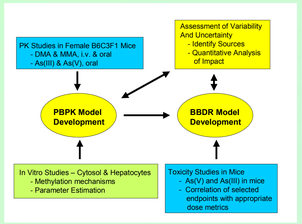
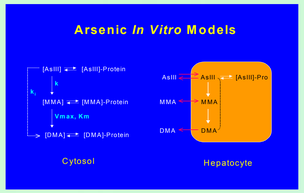
INTRODUCTION

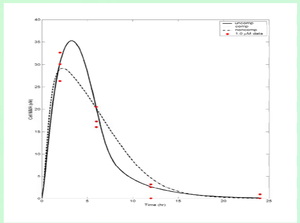
- Low dose extrapolation for As is confounded by limited understanding of the *quantitative* and *mechanistic* relationship of As target tissue dosimetry and subsequent development of adverse effects.
- Evaluation of the relationship between arsenical target tissue dosimetry and development of adverse effects is complicated by both limited tissue disposition data for inorganic As and its methylated metabolites, and studies indicating that dimethylarsinic acid (DMA(V) and the trivalent methylated arsenicals (MMA(III) and MMA(V)) have intrinsic and unique toxic effects.
- Our experimental framework integrates pharmacokinetic and pharmacodynamic model development and analysis with collection of appropriate experimental data with the goal of reducing uncertainty in arsenic low dose extrapolation.

ARSENIC PK/PD MODEL DEVELOPMENT STRATEGY

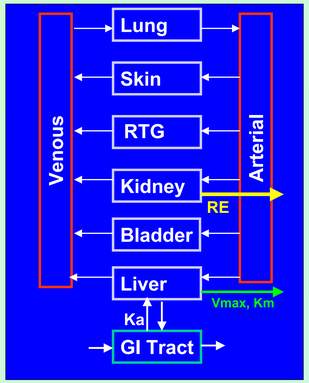


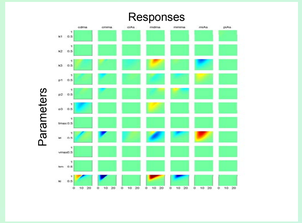
Modeling Arsenite Methylation



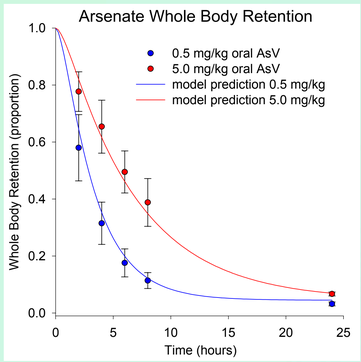


Model predictions of hepatocyte [MMA] and data (♦) for initial [iAs] = 1.0 μM. The model predictions are for uncompetitive (solid line), competitive (dotted line) and noncompetitive (dash-dot line).



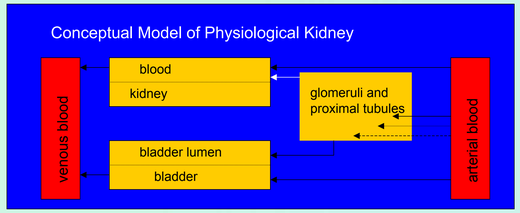


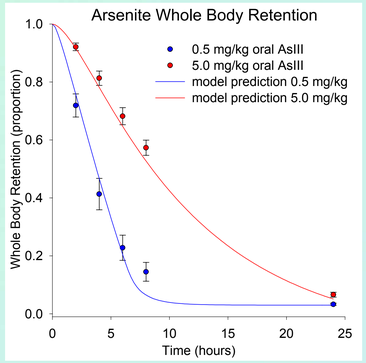
Sensitivity Analysis: Intensity plots of all 77 possible sensitivity surfaces from the hepatocyte model with uncompetitive inhibition. The eleven parameters are show in rows along the left side of the figure. The model responses are shown in columns along the top of the figure. For each individual sensitivity surface the y-axis range represents the initial [As(III)] in the media (0.1 to 1 μM) and the x-axis is the time in hours. All surfaces are plotted in the same color intensity scale to facilitate identification of influential parameters. Media arsenical concentrations were highly sensitive to their associated efflux parameters. The parameter Kt was highly influential compared to Tmax for most responses. Most parameters describing methylation and binding in the hepatocyte had very low influence.

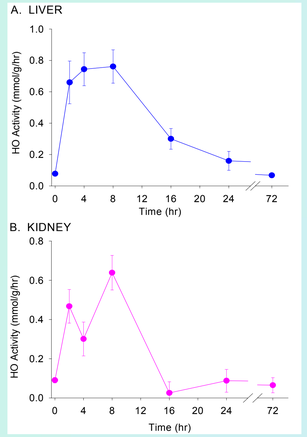


PBPK Model Structure and Parameterization

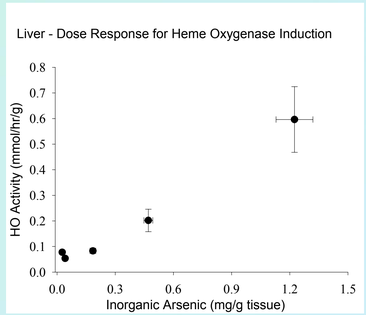
- Four separate submodels linked by reduction and methylation occurring in the liver.
- Reduction of As(V) to As(III) in GI tract.
- Distribution into most tissues is blood flow limited, with two exceptions: (1) deep lung in DMA submodel and (2) diffusion limited kidney in DMA model.
- Partition coefficients for MMA and DMA were estimated with various numerical methods using data was from our i.v. kinetic studies with MMA and DMA in mice. For As(V) and As(III) partitioning was assumed to reflect ratios reported in human tissues of individuals with background arsenic exposures.
- Physiological parameters are from published literature for mice (Brown et al., 1997).
- Oral dosing studies with As(III) were used to estimate metabolic parameters for As(III) to MMA metabolism and MMA to DMA metabolism as well as renal excretion of AsIII.
- Renal parameters for MMA and DMA were estimated using urinary excretion data from iv. kinetic studies with parent compound (Hughes & Kenyon, 1998).







Time Course for heme oxygenase (HO)activity in (A) liver and (B) kidney of mice following a single oral dose of 7.5 mg (As)/kg as Arsenite. Arsenate was a significantly less potent inducer of HO compared to arsenite and DMA was ineffective as an inducer of HO.



Correlation of mouse liver HO induction at 6 hours post exposure liver iAs concentration Data are given as mean ± S.E. (n=4-8 mice/group).

RESULTS

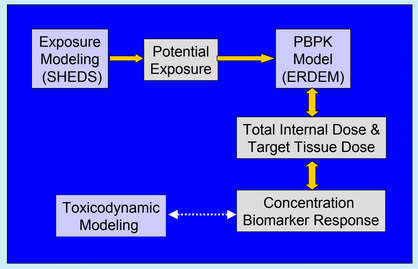
- Inhibition of the second methylation step by arsenite and binding of arsenite in liver are essential mechanisms to describe arsenic kinetics at the cellular and subcellular levels. These processes have been incorporated in the As PBPK model developed in mice.
- The strategy of using pharmacokinetic studies of individual arsenicals as a means to build and parameterize the separate submodels has been relatively successful.
- Sensitivity analysis suggests that lower doses (non-saturating) of AsV with measurement of urinary clearance and whole body retention will provide better data to estimate oral absorption and renal excretion parameters.
- The mouse PBPK model is being refined using speciated tissue data from both acute and subacute exposures in mice.
- Studies that evaluate the relationship of exposure to arsenite with markers of oxidative stress have demonstrated that levels of inorganic arsenic in liver and kidney are a sensitive and specific marker for HO induction.

IMPACT

- Utilization of PBPK model-based framework to guide experimental design and data collection has enabled the development of a biologically-based arsenic PBPK model that incorporates unique mechanisms for As metabolism and metabolite binding and sequestration.
- PBPK-BBDR model development for As provides an integrated understanding of kinetic and dynamic aspects of As toxicity that will reduce uncertainty in risk assessment.

FUTURE DIRECTIONS

- Incorporation of physiologically realistic description of the kidney and urinary bladder in ERDEM (applicable to multiple chemicals)
- Implement arsenic PBPK model with physiological kidney in ERDEM (NERL collaboration)
- Link As PBPK Model in ERDEM with SHEDS and evaluate against human exposure and epidemiologic data



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